

Infectious Diseases¹

The oral cavity is a portal of entry for many pathogens. Some of them, such as *Neisseria gonorrhoeae* and herpes zoster, enter the oral cavity and cause mainly localized disease, whereas others, such as *Treponema pallidum* and human immunodeficiency virus (HIV), proliferate locally in the oropharynx with or without apparent tissue damage and then gain entry into the bloodstream, causing systemic disease.

Diagnosis of oral infections

- A definitive diagnosis of oral infections requires the collection and critical assessment of a number of factors: clinical signs and symptoms; details of the past medical, dental, and social history; appropriate sampling and shipping of specimens; and correct interpretation of the laboratory results.
- The oral lesion could be either a purely localized infection or a secondary manifestation of a (primary) systemic infection. In the latter situation, clues related to systemic disease, such as fever, malaise, headache, sore throat, respiratory disease, joint pain, lymph node enlargement, rash, pain, and isolated lesions on other parts of the body, should be sought.
- It is also important to eliminate traumatic, neoplastic, or other immune-inflammatory diseases as they may manifest as ulceration, pain, enlarged lymph nodes, trismus, or salivary gland swellings. Although the presence or absence of pain may be useful in the differential diagnosis of oral ulcers, it should be remembered that almost any ulcer in the mouth can be painful, especially if secondarily infected by the oral flora. Hence, many oral infections present with almost identical clinical presentation, and the definitive diagnosis could be obtained only through rapid diagnostic methods and further laboratory investigations.
- Appropriate therapy should be started as soon as a provisional diagnosis has been made. As a general rule, if the patient fits into the 'classic' presentation of a particular disease, then laboratory tests are usually unnecessary, but if the signs, symptoms, or history suggest an atypical picture, or if the lesions are extensive and painful, then laboratory tests should be instituted as soon as possible. If at the next appointment the condition has not responded to treatment, the case should be critically reviewed, taking into account any available laboratory results. The review may result in a change in therapy,

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additional tests, or referral to another clinician. Due to the large number of possible pathogens that may be involved in any given oral lesion, it is important that the differential diagnosis appears on the laboratory request form. If there is doubt about which specimens are required for an investigation, the laboratory should be contacted for advice.

Bacterial infections

1. Actinomycosis

- Actinomycosis is an endogenous granulomatous disease that may occur in the cervicofacial region, abdomen and lung and peripheral skin. In humans, the main infecting organism is *Actinomyces israelii*, a gram-positive filamentous branching rod that is commonly found in plaque biofilms, carious dentine, and calculus; *Actinomyces bovis* and *Actinomyces naeslundii* may occasionally be isolated. Although most infections are monomicrobial in nature (*Actinomyces* alone causing the disease), a significant proportion of infections could be polymicrobial, with other bacteria, such as *Actinobacillus actinomycetemcomitans*, *Haemophilus* spp, and anaerobes, acting as coinfecting agents. Trauma to the jaws, tooth extraction, and teeth with gangrenous pulps may precipitate infection (calculus or plaque becoming impacted in the depths of a tooth socket at the time of extraction). Actinomycosis cannot be transmitted from human to human.

Oral considerations

- Cervicofacial actinomycosis is predominantly a disease of younger people, although all ages may be affected. The infection can present in an acute, subacute, or chronic form. There is usually a history of trauma, such as a tooth extraction or a blow to the jaw. Most infections start as an acute swelling indistinguishable on clinical grounds from a dentoalveolar abscess. The chronic form of the disease follows, due to either inadequate or no therapy or subacute infection related to trauma.
- Swelling is common and is either localized or diffuse; if untreated, it may progress into discharging sinuses. Classically, this discharge of pus contains visible granules that may be gritty to touch and yellow and are known as 'sulfur granules'. These granules in pus are almost pathognomonic of the disease.
- The submandibular region is most commonly affected; rarely, the maxillary antrum, salivary glands, and tongue may be involved. Pain is a variable feature. Other features, depending on the site of infection, are multiple

discharging sinuses, trismus, pyrexia, fibrosis around the swelling, and the presence of infected teeth.

Diagnosis and management

- If a fluctuant abscess is present, fluid pus can be collected by aspiration using a syringe or in a sterile container if drainage by external incision is performed. Examine the pus for the presence of 'sulfur granules' (yellow granular appearance); Gram films are made from any part with a lumpy or granular appearance. When crushed granules are cultured anaerobically, on blood agar, at 37°C for 7 days, colonies with a typical 'molar tooth' morphology appear. Pure cultures are then identified using biochemical techniques. A Gram film of a colony will reveal moderate to large clumps of gram-positive branching filaments. Acute lesions are managed by removal of any associated dental focus, incision, and drainage of the facial abscess and a 2- to 3-week course of antibiotics, penicillin being the drug of choice. In the case of subacute or chronic lesions, surgical intervention and a longer antibiotic course, up to 6 weeks, may be necessary. If penicillin cannot be given because of hypersensitivity, erythromycin, tetracycline, and clindamycin are good alternatives as the latter drugs penetrate bony tissues. Differential diagnosis includes tuberculosis (TB), systemic mycoses, nocardiosis, periodontal abscess and dentoalveolar abscess.

2. Mycobacterial Diseases

a. Tuberculosis

Epidemiology

- TB is the second leading cause of death by infectious disease, only surpassed by HIV infection. The World Health Organization estimates that over 8 million people develop active TB and that 2 million die each year worldwide. Ten percent of infected people will develop active TB at sometime. The potential for human to human transmission of TB through the respiratory route is extremely high.
- People with HIV/acquired immune deficiency syndrome (AIDS) are at significant risk of developing active TB after being exposed. Poverty, injection drug use, alcoholism, and homelessness have contributed to the spread of TB as large numbers of these people are in crowded shelters and/or prisons, where they are chronically exposed. Elderly people in nursing homes with declining health status are at risk for reactivating TB they were exposed to earlier in life or being newly infected when immunosuppressed. Finally, people commonly do not comply with their TB treatment regimen, which

makes them infectious longer and more likely to develop resistance to treatment.

Diagnosis

- Diagnosis is initiated by performing a tuberculin skin test on the forearm with purified protein derivative (PPD), a mycobacterial antigen. If a red welt forms within 72 hours, the patient is considered to have been exposed to *Mycobacterium tuberculosis*. This screening test is recommended for certain high-risk populations. Signs and symptoms are evaluated to look for active disease. These include productive cough, fever, chills, or night sweats. A chest radiograph is taken to look for pulmonary involvement. The final test, or acid-fast bacillus test, involves collecting patient sputum to look for the infecting organism. If present, the patient is considered to have an active infection requiring treatment.

Pathogenesis

- TB is caused by the acid- and alcohol fast bacillus *M. tuberculosis*. The organism is usually acquired by airborne transmission and grows in the pulmonary alveoli and macrophages with a local inflammatory response. In most cases, T helper cells activate macrophages through the secretion of cytokines and gamma interferon, and the infection is suppressed permanently or may remain latent to reactivate months or years later. If the immune response is compromised and cannot prevent replication of the bacteria, active disease begins. Five to 10% of exposed patients will go on to develop active TB during their life. With active infection, the following symptoms are common: chronic cough, moderate fever, night sweats, fatigue, decreased appetite, and weight loss. Occasionally, TB can spread to other parts of the body by the lymph and blood systems. Miliary (blood infection) and meningeal TB are the most serious forms of the disease, with high mortality rates.

Medical Management

- TB is curable in most patients, but compliance with drug regimens is critical to prevent reactivation of the disease or the development of resistance. The usual course of therapy is 6 to 9 months and involves several drug regimens. If patients fail initial therapy, they may have multidrug-resistant TB. If so, they will require special therapy with at least three drugs for up to 2 years. Even with this therapy, up to 60% of patients with multidrug-resistant TB will die of their disease. The directly observed therapy regimen has been extremely successful in curing recalcitrant patients and also in preventing drug-resistant strains from emerging. Adequate ventilation is the most effective measure to

prevent the spread of TB. High-risk groups are screened for TB and, if positive, treated with isoniazid (INH) for 6 to 12 months to prevent active disease. Healthcare facilities use ultraviolet light, special filters, special respirators, and masks to reduce the spread of TB. People with active TB are isolated in rooms with controlled ventilation until they are no longer infectious. There is a vaccine for TB termed bacille Calmette-Guerin (BCG), which is made from live weakened *Mycobacterium bovis*. In countries where TB is common, this vaccine is given to children with 60 to 80% efficacy. However, the vaccine is much less effective for adults, and it results in a positive skin test, reducing the effectiveness of this test in screening for TB exposure. The vaccine is not routinely used in the United States.

Oral Considerations

- Oral manifestations may occur in up to 3% of patients with long-term systemic TB. Lesions occur in the oral tissues and the neck lymph nodes. The latter is termed scrofula. The oral lesions are found in various soft tissues and supporting bone. The risk of a dental care provider acquiring TB from a patient appears to be low, particularly in a conventional dental office. Hospitals, nursing homes, prisons, and clinics that treat high risk populations are of particular concern. Patients with active TB will typically be in isolation, and dental treatment should be deferred until the patient is no longer considered infectious. Patients are no longer considered infectious if they have two consecutive negative sputum cultures or have received TB treatment for at least 2 weeks. To identify HCWs who have been exposed to TB, many hospitals require personnel to be skin-tested annually. This appears to be a reasonable practice in settings with a significant high-risk population. HCWs who have seroconverted since their last skin test are considered for 6 to 12 months of INH therapy.

b. Syphilis

- Syphilis is a classic disease with protean manifestations. There has been a significant rise in the prevalence of syphilis both in the developed and developing world during the past two decades, mainly as a disease associated with HIV infection and sexual promiscuity. Particularly striking increases have been noted in Eastern Europe, especially in the United Kingdom, and in the United States. As the prevalence of syphilis in heterosexuals has been on the rise, there has been a proportionate increase in the number of children born with congenital syphilis. Syphilis is preventable

and treatable with effective and inexpensive antibiotics; hence, its rapid diagnosis is important to prevent its late and severe sequelae. The disease is caused by *T. pallidum*, the syphilis spirochete. There is a very high likelihood of human to human transmission of syphilis through unprotected sexual activity. Syphilis has an incubation period of 10 to 90 days (average 3 weeks) and is characterized by four main clinical stages: primary, secondary, tertiary, and late or quaternary.

Primary Syphilis

- After the initial exposure to infection with *T. pallidum*, the spirochetes pass through the mucous membrane or skin and are then carried in the blood throughout the body.
- After an incubation period of about 3 to 4 weeks, there develops, at the site of entry, an ulcerated lesion called a primary chancre: a flat, red, indurated, highly infectious ulcer with a serous exudate. The typical lesion is painless, and edema of the surrounding tissues is usually present. The regional lymph nodes become enlarged about 2 weeks after the appearance of the chancre and on examination are firm, painless, and discrete, with a rubbery consistency. The chancre disappears spontaneously within 3 to 8 weeks.

Secondary Syphilis

- Approximately 2 months after healing, the secondary stage of syphilis usually develops, and in about one-third of patients, the primary chancre may be present at the same time. The signs of secondary syphilis are variable: generalized skin lesions in about 75% of cases, mucosal ulcers in about 33% of cases, generalized lymphadenopathy in about 50% of cases, and systemic symptoms that are 'influenza like,' including fever, headache, malaise, and general aches and pains. The skin lesions are found predominantly on the face, hands, feet, and genitalia and appear as dull red macular or papular spots.

Tertiary Syphilis

- Reactivation of syphilis can occur at any time 2 or 3 years after the date of first infection, but such late lesions of syphilis are rarely seen today. The characteristic lesion is the gumma, which is usually localized, single or multiple, varying in size from a pinhead to a lesion several centimeters in diameter. Gummas develop in the skin, the mucous membranes, and bones. These lesions are not infective as the tissue damage is due to a delayed type of hypersensitivity. The other organs involved in tertiary syphilis are the cardiovascular system and the nervous system.

Late or Quaternary Syphilis

- This condition is seen one to two decades after primary syphilis. The two main clinical forms of late syphilis are cardiovascular syphilis and neurosyphilis, with resultant pathology of the aorta and the nervous system, respectively.

Latent Syphilis

- This may be seen in some after many years without any symptoms. The disease lies dormant, without any clinical signs (except for positive serology), and may manifest as cardiovascular or neurosyphilis.

Congenital Syphilis

- *T. pallidum* is one of the few microorganisms that has the ability to cross the placenta! barrier; thus, the fetus may be infected during the second or third trimester from a syphilitic mother (either in the primary or secondary stage of syphilis). The disease will manifest in the infant as either (1) latent infection-no symptoms but positive serology; (2) early infection-lesions such as skin rashes, saddle nose, bone lesions, and meningitis appear up to the end of the second year of age; or (3) late infection after the second year of age; lesions include Hutchinson's incisors (notching of incisor teeth), mulberry molar teeth (due to infection of the enamel organ in the fetus), interstitial keratitis, bone sclerosis, arthritis, and deafness.

Oral Considerations

Primary Syphilis

- A chancre of the lip is the most common extragenital lesion, accounting for about 60% of cases, and may present at the angles of the mouth. Most chancres in the male tend to be located in the upper lip and in the female on the lower lip. Other sites affected are the tongue and, to a lesser extent, the gingivae and tonsillar area. Intraoral chancres are usually slightly painful due to secondary bacterial infection, as are the enlarged lymph nodes in the submaxillary, submental, and cervical regions. The lesions are infectious, and transmission may occur by kissing, unusual sexual practices, and even intermediate contact with cups, glasses, and eating utensils. The differential diagnosis of primary syphilis includes ruptured vesicles of herpes simplex, traumatic ulcers, and carcinoma.

Secondary Syphilis

- Characteristic slightly raised grayish white, glistening patches on the mucous membrane, so-called 'mucous patches,' of the tongue, soft palate, tonsil, or cheek but rarely the gingival tissues are common in the secondary stage. Lesions on the larynx and pharynx may lead to hoarseness. The surface of these lesions is covered with a grayish membrane, which can be easily

removed and contains many spirochetes. The ulcers may coalesce to give the characteristic 'snail tracks' and mucous patches in about a third of those affected. These lesions, like the primary chancre, are highly infectious. Maculopapular eruptions are confined mainly to the palate, but, occasionally, the entire oral mucosa may be involved. In recent years, the secondary syphilitic lesions found in the mouth have been noted as often atypical, due, in many cases, to inadequate treatment: as a result of antibiotic therapy for an unrelated infection. Other manifestations are generalized lymphadenopathy and condylomata (warts) of the anus and vulva; rarely, periostitis, arthritis, and glomerulonephritis *may* be seen. The differential diagnosis of secondary syphilis includes aphthous ulcers, erythema multiforme, lichen planus, and tonsillitis. The secondary-stage lesions heal 2 to 6 weeks after the time they first appear.

Tertiary Syphilis

- 'Gumma,' begins as a small, pale, raised area of the mucosa that ulcerates and rapidly progresses to a large zone of necrosis with denudation of bone and in the case of the palate may eventually perforate into the nasal cavity. The most common site for gumma formation is the hard palate, although the soft palate, lips, tongue, and face may be involved. The palatal lesions are usually midline, and in rare cases, the soft palate may be involved. Gummas are painless and have no infectivity. Occasional cases of syphilitic osteomyelitis involving the mandible and, less commonly, the maxilla have been described. This condition represents a gummatous involvement of bone with extensive necrosis. The condition is characterized by pain, swelling, suppuration and sequestration, and both clinically and radiographically, the condition may resemble pyogenic osteomyelitis. If the lesion ossifies, then the radiographic appearance of the affected area may be similar to that of an osteogenic sarcoma.
- Atrophic or interstitial glossitis is another oral manifestation of tertiary syphilis. Clinically, there is atrophy of the filiform and fungiform papillae, which results in a smooth, sometimes wrinkled lingual surface. This appearance is probably due to obliterative endarteritis of the lingual vasculature, leading to circulatory deficiency. Loss of the protective papillae subjects the dorsum of the tongue to many noxious stimuli, and leukoplakia frequently develops. The relationship between syphilitic glossitis and carcinoma of the tongue is not clear.
- Syphilis very rarely affects the salivary glands, but both secondary and tertiary lesions have been described in the parotid glands. The other main salivary

glands have also been involved either on their own or together with the parotid. Patients with general paresis of the insane may have perioral tremors and fine irregular tremors of the tongue and fingers. Although an association between oral squamous cell carcinoma and syphilis has been suggested in early studies, this relationship remains unproven.

Congenital Syphilis

- The dental lesions of congenital syphilis are a result of infection of the developing tooth germ by *T. pallidum*. Since the deciduous teeth are usually well developed by the time the spirochetes invade the developing dental tissues, these teeth are minimally affected. The permanent teeth are at an early stage of development, and infection may result in the complete failure of development of a tooth or the production of malformed teeth. Early oral manifestations include diffuse maculopapular rash, periostitis (frontal bossing of Parrot), and rhinitis, whereas late features, manifesting at least 24 months after birth, comprise the hutchinsonian triad of interstitial keratitis of the cornea, sensorineural hearing loss, and dental anomalies. The most common dental manifestation of congenital syphilis is the so-called 'mulberry molar' teeth, which are highly suggestive of prenatal syphilis. The first permanent molar teeth are usually involved and have roughened, dirty, yellow, hypoplastic, occlusal surfaces with poorly developed cusps and are smaller in size than normal. Hutchinson's incisors are another manifestation of congenital syphilis. The upper central incisors are usually involved and have crescentic notches in the middle of their incisal edge. The tooth tends to be wider gingivally than at the incisal edge, giving a 'screwdriver' appearance. The lower incisors show similar defects, but they are affected much less often than their maxillary counterparts. Of note, the maxillary incisors are more commonly affected than the mandibular ones. Infection of the developing bones of the face may lead to permanent facial deformities, which produce an open bite and a 'dished' appearance to the face. Skin around the lips may show yellow discoloration soon after birth, leading to crack formation and eventual (Parrot's) radial scars-rhagades- of the lips. Other, less common orofacial features include atrophic glossitis and a high, narrow palatal vault.

Diagnosis and Management

- Exudate from primary or secondary lesions may be collected in fine capillary tubes and examined using dark-ground microscopy for typically motile *T. pallidum*. This technique has limited value in lesions affecting the mouth since the oral commensal *Treponema microdentium* closely resembles *T. pallidum*.

However, specific immunofluorescence tests, if available, are helpful in diagnosis.

- The laboratory diagnosis of syphilis is usually made by serology since *T. pallidum* cannot be routinely cultured in vitro. Ten milliliters of venous blood is sufficient to carry out all the serologic tests for syphilis. It is usual to carry out at least two different tests on each specimen of serum, and the interpretation of these complex test results should be left to an expert in genitourinary infections. Antigens used for syphilis serology are of two types:
 - *Cardiolipin or lipoidal antigen*. Although not derived from the spirochete, it is sensitive for detecting antibody. The most popular test that uses this antibody is the VDRL (Venereal Diseases Reference Laboratory) test; it is simple and sensitive, but biologic false-positive reactions are common. As the antibody disappears after treatment, it can be used to monitor the efficacy of antimicrobial therapy.
 - *Specific treponemal antigen*. Using *T. pallidum* as an antigen gives fewer false-positive reactions, and tests remain positive after treatment. The tests are *T. pallidum* hemagglutination test, fluorescent treponemal antibody-absorption test (FTA-Abs) which detects both IgM and IgG antibody, and ELISA. The last is increasingly used as a screening test to detect IgG antibody, although some false positives may result.

Differential Diagnosis

- Primary and secondary syphilis include candidiasis, leukoplakia, hairy leukoplakia, lichen planus, aphthous ulcers, herpetic gingivostomatitis, erythema multiforme, TB, and trauma. The most effective drug for syphilis is procaine benzylpenicillin. Doxycycline or erythromycin can be used in patients who are sensitive to penicillin. Follow-up with regular clinical and serologic examinations is necessary for at least 2 years.

Viral infections

1. Viral Hepatitis

- Approximately 80% of viral hepatitis infections are caused by hepatitis A (HAV), hepatitis B (HBV), hepatitis C (HCV), hepatitis D (HDV), or hepatitis E (HEV). As a consequence of their parenteral mode of transmission and ability to establish chronic infection, hepatitis types HBV, HDV, and HCV are of particular concern for oral health care professionals. HAV and HEV are predominantly spread through enteral modes and do not incur chronic disease.

Epidemiology

- HBV, HDV, and HCV all exhibit significant genetic diversity as evidenced by traceable geographic distributions. From a clinical perspective, genotype assessment is useful for monitoring the clinical course, directing therapeutic interventions, and, ultimately, predicting prognosis of infection. For HBV, there are eight genotypes (A-H) and numerous subgenotypes and hepatitis B surface antigen (HbsAg) subtypes. HDV is a defective virus that requires the simultaneous presence of HBV to establish infection, and three distinct genotypes are recognized. For HCV, there are six genotypes and numerous subtypes.
- These viruses are all spread via contact with contaminated blood. Vertical transmission from an infected mother to child accounts for most cases of HBV infection worldwide. For children born of infected mothers who are hepatitis B e antigen (HBeAg is a serologic marker for viral replication) negative, the risk is 10 to 40%, whereas for children born of mothers who are HBeAg positive, the risk is 70 to 90%. Child to child transmission can also occur. Transmission via the aforementioned routes has decreased dramatically in the industrialized world, in large part due to the implementation of aggressive vaccination and screening programs. Other major risk factors for HBV infection include having multiple sex partners, sex with HBV-infected persons, and intravenous drug use. The risk of developing chronic HBV infection correlates well with the patient's age at initial infection. Thus, neonates, whose immune systems are immature, have a 90% chance of developing chronic HBV infection, compared with a 30% chance for children aged 1 to 5 years and a 5% chance for adults.
- The predominant risk factors for HDV infection are intravenous drug use, sex with an infected partner, and exposure to blood products prior to 1992. Infection may occur simultaneously with an HBV infection (coinfection) or as a new infection affecting a patient with chronic HBV (superinfection). Chronicity is more likely to occur as a consequence of superinfection.
- For HCV, the predominant route of transmission is intravenous drug use, accounting for 50% of cases. Mother to child transmission risk is estimated to be about 4 to 7%, with a four- to fivefold increase noted if the mother is also coinfecting with HIV. Other risk factors for HCV infection include exposure to blood products prior to 1992, undergoing unsanitary medical procedures, having sex with an infected partner, and household contact. Approximately 50 to 85% of patients acutely infected with HCV subsequently develop chronic infection. The worldwide disease burden of viral hepatitis is significant, and there is extensive geographic variation. Over 2 billion people

have been infected with HBV, with an estimated 350 million manifesting chronic infection. Chronic infection rates are highest in sub-Saharan Africa, most of Asia, and the Pacific (8-10%) and lowest in western Europe and North America. For HDV and HCV, the worldwide estimates for chronic infection are 10 million and 170 million people, respectively. Most cases of HDV infection affect those living in the Eastern Mediterranean. Prevalence rates for HCV are highest in Africa and the Eastern Mediterranean (> 4.5%) and lowest in Europe (1.0%).

Diagnosis

- For both acute and chronic forms of viral hepatitis, many patients have either no symptoms or symptoms so mild as to be easily overlooked (fatigue, nausea, fever, abdominal pain, loss of appetite). As a consequence, hepatitis is often discovered during routine laboratory screening as part of a physical examination or voluntary blood donation. The likelihood of developing symptomatic illness is inversely related to one's age at the time of infection. The more characteristic signs and symptoms of jaundice, urticaria, dark-colored urine, light-colored stools, and an enlarged/tender liver signal the presence of more extensive liver damage. Other conditions to consider in the differential diagnosis include alcohol abuse, fatty liver, autoimmune hepatitis, primary biliary cirrhosis, hemochromatosis, Wilson's disease, and (α_1 -antitrypsin deficiency).
- Laboratory testing is essential for establishing the diagnosis, monitoring disease progression, and assessing the results of therapeutic interventions. Basic liver function tests include alanine aminotransferase, alkaline phosphatase, aspartate aminotransferase, albumin, and total protein. Although useful, liver function tests must be correlated with specific serologic tests to establish etiology. For HBV, available tests include HBsAg, HBV surface antibody (anti-HBs), HBeAg, HBV e antibody (anti-HBe), and HBV core antibody (anti-HBc and IgM anti-HBc). For HDV, HDV antigen (HDAg) and HDV antibody (anti-HD) may be obtained. For HCV, the only routinely ordered test is for HCV antibody (anti-HCV). Viral load testing for all three viruses is available and useful in assessing disease status, as is liver biopsy.

Pathogenesis

- The pathogenic mechanisms of HBV, HDV, and HCV are only partially understood, and numerous factors, such as route of transmission, viral subtype, and the patient's age, immunocompetence, and health, influence pathogenesis.

- Although these viruses are hepatotropic, they do not appear to be directly cytopathic, and the severity of hepatocyte injury reflects the intensity of the host cellular immune response.
- Patients who develop a vigorous cytotoxic T-cell response to infection are more likely to manifest severe, at times fulminant, liver injury, but they are at low risk of developing chronic infection. In contrast, patients who generate a less vigorous cytotoxic T-cell response to infection manifest little acute liver injury but are at much greater risk for developing chronic infection. Putative mechanisms underlying the ability of these viruses to circumvent the host immune response and establish chronic infection include the suppressive actions of viral antigens on the host immune system, reduced CD4 T-cell help, the suppressive effects of T-regulatory cells, and the high rate of viral mutation.
- Chronic infection is a dynamic process for which the outcome varies from patient to patient. Some patients manifest no symptoms throughout their lives; others manifest only occasional flares of clinical illness; and still others experience unrelenting progressive clinical illness. The two main concerns related to chronic viral hepatitis are the increased risks for developing cirrhosis and hepatocellular carcinoma (HCC). The association between chronic viral hepatitis and HCC, although strong, is poorly understood. A multitude of factors that possibly contribute to the development of HCC include direct virus-induced mutagenesis, the accumulation of genetic and epigenetic lesions associated with continuous hepatocyte necrosis and regeneration, and an increased susceptibility to the carcinogenic actions of aflatoxins and alcohol. For patients with chronic HBV, the risk of developing cirrhosis or HCC is 15 to 40%. Contributing factors include male sex, infection at an early age, heavy alcohol consumption, coinfection with other hepatotropic viruses or HIV, immunosuppression, and high HBV viral loads. For chronic HCV infection, 2 to 20% of patients develop cirrhosis typically over a period of 20 to 30 years. Once cirrhosis occurs, 1 to 4% of patients with chronic HCV develop HCC each year. For chronic HDV, progression to cirrhosis typically occurs within 5 to 10 years and affects 60 to 70% of patients.

Medical Management

- Treatment protocols for acute viral hepatitis are supportive, and there is no consensus on the value or need to provide antiviral therapy during an acute infection. For chronic viral hepatitis, the decision on how and when to institute therapy is complex and must be based on factors such as patient interest, clinical and laboratory findings, risk of disease progression without

intervention, odds of therapeutic success, risk of therapeutic adverse effects, and the overall health of the patient. The goals of therapy are to slow the progression to cirrhosis, prevent hepatic failure, and prevent the development of HCC. For patients with advanced disease, in whom medical therapy is either ineffective or contraindicated, the only remaining option is liver transplantation.

- Approved drug therapies to treat chronic HBV include interferon- α 2b, pegylated interferon- α 2a, adefovir dipivoxil, lamivudine, and entecavir. Since these drugs do not eradicate HBV, therapeutic protocols tend to be prolonged. Interferon- α 2b and pegylated interferon- α 2a are biologic response modifiers that enhance the host's natural immune response.
- Adefovir dipivoxil, lamivudine, and entecavir are nucleoside analogues that inhibit HBV DNA synthesis. The emergence of resistant HBV strains is of particular concern for lamivudine, reaching 32% after 1 year and 70% after 5 years of therapy. Overall, about two-thirds of patients who qualify for antiviral therapy enter an inactive phase, marked by HBeAg seroconversion and a drop in HBV DNA viral load below 3 log₁₀ IU/mL. However, 20% will suffer relapse later in life. Current therapeutic strategies to control chronic HBV infection are ineffective.
- Drugs available for the treatment of HCV are pegylated interferon- α and ribavirin. Therapeutic success results in a sustained virologic response (SVR) and is largely predicated on the HCV genotype and the pretreatment HCV viral load. SVR rates are highest for patients who are under 40 years of age, weigh less than 75 kg, have genotype 2 or 3 HCV infections, and have low pretreatment viral loads. Patients with genotype 1 HCV infection are less responsive to therapy. The overall SVR rate is about 40%. Preventive measures to reduce viral hepatitis spread include aggressive vaccination protocols (for HBV); adequate screening and handling measures for donated blood and tissues; the implementation of proven infection control measures in the health care setting; and promotional/educational efforts to reduce the practice of unsafe injection drug use and/or high-risk sexual practices. Approximately 90% of healthy adults and 95% of infants, children, and adolescents produce protective antibodies against HBV after vaccination. An adequate response is defined as a serum level of anti-HBs antibody of ≥ 10 mIU/mL. Although some waning of the anti-HBs response may occur over time, clear guidelines regarding the need for booster immunization have yet to be established. Unfortunately, there exists no vaccine against HCV.

Oral Health Considerations

- Prior to initiating therapy, the clinician should ascertain the patient's overall status with attention focused on the patient's potential for increased hemorrhage and impaired drug metabolism. In general, ambulatory patients who do not manifest signs and symptoms of active disease and are not under active medical therapy will tolerate the delivery of routine dental care. However, if there is doubt as to the patient's status, it is prudent to consult the treating physician in order to develop a treatment plan for the patient that is safe and appropriate.
- Pertinent laboratory testing includes complete blood count, prothrombin time, partial thromboplastin time, international normalized ratio, bleeding time, and liver function tests. Clinical clues of impaired liver function include jaundice, easy hemorrhage, and the presence of petechiae, hematomas, or ecchymoses. Additional clues to the presence of liver disease include Dupuytren's contracture, palmar erythema, edema, urticaria, gynecomastia, spider nevi, and sialosis.
- Patients with severe liver impairment are best managed in a hospital setting, where close monitoring and indicated supplemental therapies, such as fresh frozen plasma, may be provided. All drugs metabolized by the liver should be avoided when possible or administered cautiously to patients with severely impaired liver function.
- As blood borne agents, HBV, HCV, and HDV pose serious occupational concerns for HCWs, in whom there is a risk of patient to HCW, HCW to patient, and patient to patient transmission. The risk of infection is influenced by the route of exposure, the concentration of infectious virions in the source body fluid, and the volume of infected material transferred. For HBV, the risk has been reduced dramatically through HBV vaccination programs. Prior to the availability of HBV vaccination, an estimated 10,000 HCWs became infected annually in the United States. For 2002, the estimated number of cases affecting HCWs had fallen to 400. Another benefit of HBV vaccination is prevention of HDV infection since HDV requires the presence of HBV to establish infection. However, since HBV vaccination is not universally effective and there exists no vaccine for HCV, HCWs must strictly follow established infection control recommendations to minimize the risk of occupational transmission. For HCWs who either decline HBV vaccination or fail to seroconvert, the risk of HBV infection after a percutaneous exposure is 37 to 62% if the source is HBeAg positive and 23 to 37% if the source is HBeAg negative. For such scenarios, postexposure prophylaxis with hepatitis B immunoglobulin is effective 75% of the time in preventing infection if

prescribed within 1 week of exposure. The risk of occupationally acquiring HCV from an infected patient appears to be much less than HBV, with reported rates of seroconversion ranging from 0.0 to 7.0% after percutaneous exposure. However, no prophylactic postexposure protocols exist. Patient to patient transmission of viral hepatitis occurs as a consequence of cross-contamination and is unlikely to occur in the dental setting when adequate infection control measures are followed. The risk of an HCW infected with viral hepatitis cross-infecting a patient in the occupational setting is fortunately low. In general, HBV-infected practitioners who are deemed highly infectious should not practice exposure-prone procedures. The two indicators of high HBV infectivity are the presence of HB Ag in the serum or a high viral load of HBV DNA. However, there exists a variant of HBV (precore mutant) that does not express HBeAg but is still capable of producing a high viral load of HBV DNA. The HBV DNA viral load is considered as the best measure of infectivity. Since the risk of HCV transmission from an infected HCW to a patient is low, most authorities do not recommend preemptive practice limitations.

2. Human Immunodeficiency Virus (HIV)

Epidemiology

- There exist two recognized types of HIV: HIV-1 and HIV-2. Both have the same modes of transmission, and both may cause immunosuppression and AIDS. However, compared with HIV-1, HIV-2 rarely occurs outside Africa and tends to follow a more indolent clinical course. HIV-1 is further classified into three groups: M, N, and O.
- The prime modes of transmission for HIV are (1) unprotected penetrative sex between men, (2) unprotected heterosexual intercourse, (3) injection drug use, (4) unsanitary injections and blood transfusions, and (5) mother to child spread during pregnancy, delivery, or breast-feeding.

Diagnosis

- The diagnosis of HIV infection is obtained by appropriate laboratory testing. In the standard HIV-antibody test algorithm, a plasma or serum sample is subjected to an EIA; if the result is positive, a second EIA is performed; and if that result is positive, a confirmatory Western blot analysis is performed. This algorithm is highly sensitive and specific, with reported false-positive rates. However, cases of recent HIV infection may be missed as it takes several weeks (even months) for a measurable antibody response to develop. As a consequence, several other testing methods targeting HIV antigen identification have been developed. New testing protocols using saliva, urine, and finger-prick testing, along with rapid tests, yield tentative results in

as little as 20 minutes. Determining who should be tested for HIV infection represents an area of ongoing debate. In the past, only patients at high risk for exposure to HIV (ie, injection drug users, men having sex with men, sexually active men and women with multiple partners) or those presenting with signs and symptoms suggestive of HIV infection were recommended for testing.

Pathogenesis

- For untreated HIV infection, a common pattern of disease progression has been established consisting of three phases: (1) primal infection, (2) prolonged (median = 10 years) period of clinical latency, and (3) the appearance of clinically apparent disease. A dynamic process in which the initial and ongoing immunologic response to HIV infection is not only unsuccessful in clearing the HIV but is paradoxically paralleled by a progressive reduction in immunocompetence and eventual development of AIDS. HIV is a spherically shaped retrovirus whose outer coat, or envelope, consists of two layers of fatty molecules called lipids. These lipids are actually taken from the human cell membrane when newly formed virus particles bud from the cell. Protruding from the envelope are approximately 72 sets of a complex HIV protein known as Env. Env consists of a stem consisting of three glycoprotein (gp) molecules called gp41 and a cap consisting of three glycoprotein molecules called gp 120. Both gp 120 and gp41 are essential for the recognition and binding of target cells. Within the envelope is the bullet-shaped core or capsid, which consists of about 2,000 copies of the HIV protein p24. The capsid encircles two single strands of HIV ribonucleic acid (RNA) and the enzymes reverse transcriptase, integrase, and protease.
- The predominant portal of entry for HIV is through blood and/or mucosal exposure. The virus can enter through various mucosal surfaces, including the linings of the vagina, vulva, rectum, penis, or, rarely, oral cavity. Infection is enhanced in scenarios where the mucosal tissues are ulcerated or inflamed. Dendritic cells within the mucosa, which normally process and present antigen to immune cells, express a molecule called DC-SIGN, which has a high affinity for HIV gp120. HIV virions bound to DC-SIGN are compartmentalized and, upon migration of the dendritic cells to the lymph nodes, subsequently regurgitated and presented to T cells. In this fashion, dendritic cells appear to act as a Trojan horse to facilitate infection.
- Upon initial infection, a rapid sequence of virologic, immunologic, and clinical events occurs within the first 4 to 8 weeks of infection (i.e., primary infection). There is a rapid rise in plasma viremia and seeding of the virus in

lymphoid tissues throughout the body. A firestorm of immunologic activity occurs during this period, highlighted by the production of an estimated 10 billion virions per day (half life = 1.6 days) combined with the destruction and replacement of about 2 billion CD4+ lymphocytes per day. Although many individuals experience minimal symptoms, an estimated 40 to 90% experience an acute viral syndrome characterized by varying degrees of fever, fatigue, maculopapular rash, headache, lymphadenopathy, pharyngitis, myalgia, arthralgia, gastrointestinal distress, night sweats, and oral or genital ulcers. Unlike most infections, the normal immune response associated with HIV infection produces confounding detrimental effects since (1) newly generated CD4+ lymphocytes represent new targets for HIV infection and (2) increased production of pro inflammatory cytokines (i.e., tumor necrosis factor α and interleukin-6) may promote viral expression. Eventually, a virus-specific cell-mediated immune response (CD8+ lymphocyte) acts to partially dampen the viremia. The cellular response is subsequently followed by the production of HIV-neutralizing antibody. The dampening of viremia to a lowered viral setpoint corresponds to the beginning of the period of clinical latency. However, although the level of viral burden in peripheral blood mononuclear cells is reduced, it remains 1,000 times higher in the lymphoid tissue. In general, the higher the viral setpoint, the more rapid the progression to AIDS. However, the overall variability regarding the rate of natural disease progression is high. An estimated 10% of patients develop AIDS within 2 to 3 years of exposure to HIV, whereas 10 to 17% of HIV-infected patients may not develop AIDS even 10 years after exposure. The manner in which HIV successfully persists and ultimately overwhelms the host's immune system likely results from a multitude of factors, such as host genetic predisposition, viral pathogenicity, high viral mutation rates, perturbations of antigen processing and presentation, immunologic sanctuary, and proviral latency.

Medical Management

- The initial patient workup of the HIV-infected patient should identify the state of current infection (acute or chronic) and the presence of co-morbidities. It consists of a complete medical history, physical examination, and laboratory evaluation. Essential laboratory tests include HIV antibody testing, CD4+ count, and plasma HIV RNA (viral load). Medical therapy is essentially two pronged, targeting the opportunistic infections associated with immunosuppression and the HIV itself. This chapter limits its discussion to the antiretroviral arm of therapy.

- The decision to initiate antiretroviral therapy is primarily based on the baseline CD4⁺ count and viral load. In general, antiviral therapy is recommended for any patient with a history of an AIDS-defining illness, regardless of CD4⁺ counts, or any asymptomatic patient with a CD4⁺ count < 200 cells/mm³. The efficacy of antiretroviral therapy is determined by frequent monitoring of both the CD4⁺ count and the viral load. Available antiretroviral drugs target structural and functional differences between viral and human proteins. Four classes exist: (1) fusion inhibitors, (2) nucleoside reverse transcriptase inhibitors (NRTIs), (3) non-nucleoside reverse transcriptase inhibitors (NNRTIs), and (4) protease inhibitors (PIs). The fusion inhibitor enfuvirtide (T20) is an anti-HIV peptide structurally similar to HIV gp41 and competitively inhibits viral entry into host cells. NRTIs mimic deoxyribonucleoside triphosphate, the natural substrate for reverse transcriptase. As they become incorporated into the growing DNA chain, they terminate elongation and decrease or prevent HIV replication in infected cells. NRTIs include abacavir (ABC), didanosine (ddI) and zidovudine (AZT, ZDV). NNRTIs bind near the catalytic site of reverse transcriptase and inhibit a crucial step in the transcription of the RNA genome into a double-stranded retroviral DNA.
- NNRTIs include delavirdine (DLV), efavirenz (EFV), and nevirapine (NVP). PIs block the cleavage of viral proteins during assembly and maturation, a process essential for the newly formed virus to become infectious. PIs include amprenavir (APV).
- The treatment of HIV infection requires combination therapy known as highly active antiretroviral therapy (HAART). Antiretroviral regimens currently recommended for the treatment of naive patients may be NNRTI based (1 NNRTI+2 NRTIs), PI based (1 or 2 PIs+2 NRTIs), or triple NRTI based (3 NRTIs). The treatment of patients with acute HIV infection, HIV-infected adolescents, injection drug users, HIV-infected women of reproductive age and pregnant women, and patients with coinfections (HBV, HCV, and tuberculosis) requires special antiretroviral regimens.
- Although HAART can dampen viremia, delay disease progression, and thus prolong and improve the quality of life for the HIV-infected patient, it is not curative and not a panacea to address the worldwide HIV burden. Furthermore, HAART drugs are expensive, rendering them unavailable for much of the infected population; they often incur significant toxicity and serious adverse drug interactions; their use is frequently compliance intense; and the emergence of drug resistance remains a serious concern. Potentially serious or life-threatening adverse reactions associated with antiretroviral

therapy are usually drug specific and include bleeding episodes, bone marrow suppression, hepatotoxicity, hepatic necrosis, hypersensitivity reactions, lactic acidosis, nephrolithiasis, nephrotoxicity, pancreatitis, and Stevens-Johnson syndrome/toxic epidermal necrolysis. Although HAART usually results in improved CD4+ counts and decreased viral load, a subset of patients experience a paradoxical condition termed immune reconstitution inflammatory syndrome (IRIS). In these patients, HAART-induced immune recovery results in a spectrum of presentations ranging from clinical worsening of established opportunistic infection and the appearance of new opportunistic infections to autoimmune disorders. Most cases of IRIS manifest themselves within the first few months of HAART, and those at highest risk are patients with low baseline CD4+ counts and/or an underlying opportunistic infection when HAART is initiated.

- There are no oral lesions that are specific to HIV infected patients. However, numerous oral lesions have been documented to occur in association with the HIV-induced immunosuppression. Oral lesions are either (1) strongly associated with, (2) less commonly associated with, or (3) simply seen with HIV infection. The most strongly associated lesions in adult patients are candidiasis (erythematous, pseudomembranous), hairy leukoplakia, Kaposi's sarcoma, non-Hodgkin's lymphoma, and periodontal disease (linear gingival erythema, necrotizing ulcerative gingivitis, necrotizing ulcerative periodontitis). For pediatric patients, the most strongly associated lesions are candidiasis (erythematous, pseudomembranous, angular cheilitis), herpes simplex infection, linear gingival erythema, parotid enlargement, and recurrent aphthous stomatitis (minor, major, herpetiform). The risk of developing these lesions is inversely related to the CD4+ counts. Thus, these lesions often serve as good clinical markers signaling a loss in therapeutic efficacy of HAART.

Oral health considerations

- Dental practitioners should anticipate that HIV-infected patients will seek care either for their routine dental concerns or oral conditions associated with their underlying disease. Prior to initiating therapy, the clinician should ascertain the patient's immune status, presence of co-morbidities, current medication profile, and prognosis.
- The most pertinent criteria related to the provision of oral health care are the CD4+ count, HIV viral load, neutrophil count, platelet count, and the medications the patient is taking. As with other medically complex patients, significant concerns for the HIV-infected patient are impaired hemostasis,

susceptibility to dentally induced infection, adverse drug effects /interactions, and the patient's ability to tolerate the stresses associated with the delivery of dental care.

- In general, HIV-infected patients presenting in the outpatient dental setting are sufficiently healthy to tolerate the full spectrum of modern dental services. The goals of therapy should be to optimize oral hygiene and function, establish a recall schedule, monitor for and manage HIV-associated oral lesions, and monitor for and manage drug-induced oral side effects, such as xerostomia.
- There are no evidence-based studies demonstrating either a need or justification for the routine use of antimicrobial prophylaxis to reduce the occurrence of a bacteremia arising from routine dental procedures in the HIV-infected patient. An indication where antimicrobial prophylaxis is empirically recommended is neutropenia (i.e., neutrophil counts $<500/\text{mm}^3$). Patients with low platelet counts (i.e., $<50,000$ cells/ mm^3) are at risk for increased bleeding and should be managed accordingly.
- The medication profile for the HIV-infected patient is typically complex, reinforcing the obligation of the dental practitioner to routinely monitor for adverse drug effects/interactions. Common side effects that may require modification of routine dental protocols include hepatotoxicity, hyperglycemia, and an increased susceptibility for coronary artery disease. HAART appears to modulate, but not eradicate, the risk of oral lesions in the HIV-infected patient. It is postulated that an increased occurrence of some oral conditions, such as oral warts, salivary gland enlargement, and dry mouth, may represent the oral consequences of IRIS. Management protocols for a specific oral lesion or condition are discussed elsewhere in the text.
- The transmission of HIV infection from patients to health care personnel (HCP) may occur after percutaneous (cut with a sharp instrument or needle stick) and, infrequently, mucocutaneous exposure to blood and other body fluids containing blood. The risk of infection among HCP following percutaneous exposure to HIV-infected blood was more likely (1) in the presence of visible blood on the instrument before injury; (2) if the injury involved a needle, which was placed directly into the patient's vein or artery; (3) if the injury caused by the contaminated instrument or needle was deep; or (4) if the source patient has an increased viral load, that is, was terminally ill. The average risk for HIV infection after percutaneous and mucous membrane (eyes, nose, mouth) exposure to HIV-infected blood is approximately 0.3 and 0.09%, respectively. The transmission of HIV infection after nonintact skin

exposure is estimated to be less than the risk following mucous membrane exposure. Similarly, the risk of transmission after exposure to fluids or tissues other than HIV-infected blood is probably considerably lower than the risk following exposure to blood. When adequate infection control precautions are observed, the risk of HIV transmission in the oral health care setting is extremely low.